



THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence

Citation for published version:

Savage, JE, Jansen, PR, Stringer, S, Watanabe, K, Bryois, J, De Leeuw, CA, Nagel, M, Awasthi, S, Barr, PB, Coleman, JRI, Grasby, KL, Hammerschlag, AR, Kaminski, JA, Karlsson, R, Krapohl, E, Lam, M, Nygaard, M, Reynolds, CA, Trampush, JW, Young, H, Zabaneh, D, Hägg, S, Hansell, NK, Karlsson, IK, Linnarsson, S, Montgomery, GW, Muñoz-manchado, AB, Quinlan, EB, Schumann, G, Skene, NG, Webb, BT, White, T, Arking, DE, Avramopoulos, D, Bilder, RM, Bitsios, P, Burdick, KE, Cannon, TD, Chiba-falek, O, Christoforou, A, Cirulli, ET, Congdon, E, Corvin, A, Davies, G, Deary, IJ, Derosse, P, Dickinson, D, Djurovic, S, Donohoe, G, Conley, ED, Eriksson, JG, Espeseth, T, Freimer, NA, Giakoumaki, S, Giegling, I, Gill, M, Glahn, DC, Hariri, AR, Hatzimanolis, A, Keller, MC, Knowles, E, Koltai, D, Konte, B, Lahti, J, Le Hellard, S, Lencz, T, Liewald, DC, London, E, Lundervold, AJ, Malhotra, AK, Melle, I, Morris, D, Need, AC, Ollier, W, Palotie, A, Payton, A, Pendleton, N, Poldrack, RA, Rääkkönen, K, Reinvang, I, Roussos, P, Rujescu, D, Sabb, FW, Scult, MA, Smeland, OB, Smyrnis, N, Starr, JM, Steen, VM, Stefanis, NC, Straub, RE, Sundet, K, Tiemeier, H, Voineskos, AN, Weinberger, DR, Widen, E, Yu, J, Abecasis, G, Andreassen, OA, Breen, G, Christiansen, L, Debrabant, B, Dick, DM, Heinz, A, Hjerling-leffler, J, Ikram, MA, Kendler, KS, Martin, NG, Medland, SE, Pedersen, NL, Plomin, R, Polderman, TJC, Ripke, S, Van Der Sluis, S, Sullivan, PF, Vrieze, SI, Wright, MJ & Posthuma, D 2018, 'Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence', *Nature Genetics*, vol. 50, pp. 912-919. <https://doi.org/10.1038/s41588-018-0152-6>

Digital Object Identifier (DOI):

[10.1038/s41588-018-0152-6](https://doi.org/10.1038/s41588-018-0152-6)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Nature Genetics

General rights

Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 04. May. 2023



Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence

Jeanne E Savage^{1#}, Philip R Jansen^{1,2#}, Sven Stringer¹, Kyoko Watanabe¹, Julien Bryois³, Christiaan A de Leeuw¹, Mats Nagel⁴, Swapnil Awasthi⁵, Peter B Barr⁶, Jonathan R I Coleman^{7,8}, Katrina L Grasby⁹, Anke R Hammerschlag¹, Jakob A Kaminski^{5,10}, Robert Karlsson³, Eva Krapohl⁷, Max Lam¹¹, Marianne Nygaard^{12,13}, Chandra A Reynolds¹⁴, Joey W Trampush^{15,16}, Hannah Young¹⁷, Delilah Zabaneh⁷, Sara Hägg³, Narelle K Hansell¹⁸, Ida K Karlsson³, Sten Linnarsson¹⁹, Grant W Montgomery^{9,20}, Ana B Muñoz-Manchado¹⁹, Erin B Quinlan²¹, Gunter Schumann²¹, Nathan G Skene^{19,22}, Bradley T Webb^{23,24}, Tonya White², Dan E Arking²⁵, Dimitrios Avramopoulos^{25,26}, Robert M Bilder²⁷, Panos Bitsios²⁸, Katherine E Burdick^{29,30,31}, Tyrone D Cannon³², Ornit Chiba-Falek³³, Andrea Christoforou³⁴, Elizabeth T Cirulli³⁵, Eliza Congdon²⁷, Aiden Corvin³⁶, Gail Davies^{37,38}, Ian J Deary^{37,38}, Pamela DeRosse^{39,40,41}, Dwight Dickinson⁴², Srdjan Djurovic^{43,44}, Gary Donohoe⁴⁵, Emily Drabant Conley⁴⁶, Johan G Eriksson^{47,48}, Thomas Espeseth^{49,50}, Nelson A Freimer²⁷, Stella Giakoumaki⁵¹, Ina Giegling⁵², Michael Gill³⁶, David C Glahn⁵³, Ahmad R Hariri⁵⁴, Alex Hatzimanolis^{55,56,57}, Matthew C Keller⁵⁸, Emma Knowles⁵³, Deborah Koltai⁵⁹, Bettina Konte⁵², Jari Lahti^{60,61}, Stephanie Le Hellard^{34,44}, Todd Lencz^{39,40,41}, David C Liewald³⁸, Edythe London^{27,62}, Astri J Lundervold^{63,64}, Anil K Malhotra^{39,40,41}, Ingrid Melle^{44,50}, Derek Morris⁴⁵, Anna C Need⁶⁵, William Ollier⁶⁶, Aarno Palotie^{67,68,69}, Antony Payton⁷⁰, Neil Pendleton⁷¹, Russell A Poldrack⁷², Katri Räikkönen⁷³, Ivar Reinvang⁴⁹, Panos Roussos^{29,30,74}, Dan Rujescu⁵², Fred W Sabb⁷⁵, Matthew A Scult⁵⁴, Olav B Smeland⁷⁶, Nikolaos Smyrnis^{55,56}, John M Starr^{37,77}, Vidar M Steen^{34,44}, Nikos C Stefanis^{55,56,57}, Richard E Straub⁷⁸, Kjetil Sundet^{49,50}, Henning Tiemeier^{2,79}, Aristotle N Voineskos⁸⁰, Daniel R Weinberger⁷⁸, Elisabeth Widen⁶⁷, Jin Yu³⁹, Goncalo Abecasis^{81,82}, Ole A Andreassen^{50,76,83}, Gerome Breen^{7,8}, Lene Christiansen^{12,13}, Birgit Debrabant¹³, Danielle M Dick^{6,84,85}, Andreas Heinz⁵, Jens Hjerling-Leffler¹⁹, M Arfan Ikram⁷⁹, Kenneth S Kendler^{23,24,84}, Nicholas G Martin⁹, Sarah E Medland⁹, Nancy L Pedersen³, Robert Plomin⁷, Tinca JC Polderman¹, Stephan Ripke^{5,86,87}, Sophie van der Sluis⁴, Patrick F Sullivan^{3,88}, Scott I Vrieze¹⁷, Margaret J Wright^{18,89}, Danielle Posthuma^{1,4*}

Affiliations:

1. Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
2. Department of Child and Adolescent Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands
3. Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
4. Department of Clinical Genetics, section Complex Trait Genetics, Neuroscience Campus Amsterdam, VU Medical Center, Amsterdam, the Netherlands
5. Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Campus Mitte, Berlin, Germany
6. Department of Psychology, Virginia Commonwealth University, Richmond, VA, USA
7. Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
8. NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Trust, London, UK
9. QIMR Berghofer Medical Research Institute, Herston, Brisbane, Australia
10. Berlin Institute of Health (BIH), 10178 Berlin, Germany
11. Institute of Mental Health, Singapore
12. The Danish Twin Registry and the Danish Aging Research Center, Department of Public Health, University of Southern Denmark, Odense, Denmark
13. Epidemiology, Biostatistics and Biodemography, Department of Public Health, University of Southern Denmark, Odense, Denmark
14. Department of Psychology, University of California Riverside, Riverside, California, USA

15. BrainWorkup, LLC, Los Angeles, California, USA
16. Department of Psychiatry and the Behavioral Sciences, Keck School of Medicine, University of Southern California, Los Angeles, California, USA
17. Department of Psychology, University of Minnesota, Saint Paul, Minnesota, USA
18. Queensland Brain Institute, University of Queensland, Brisbane, Australia
19. Laboratory of Molecular Neurobiology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden
20. Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia
21. Centre for Population Neuroscience and Precision Medicine (PONS), Institute of Psychiatry, Psychology and Neuroscience, MRC-SGDP Centre, King's College London, London, UK
22. UCL Institute of Neurology, Queen Square, London, UK
23. Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA
24. Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA
25. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
26. Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
27. UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, California, USA
28. Department of Psychiatry and Behavioral Sciences, Faculty of Medicine, University of Crete, Heraklion, Crete, Greece
29. Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA
30. Mental Illness Research, Education, and Clinical Center (VISN 2), James J. Peters VA Medical Center, Bronx, New York, USA
31. Department of Psychiatry - Brigham and Women's Hospital; Harvard Medical School; Boston MA
32. Department of Psychology, Yale University, New Haven, Connecticut, USA
33. Department of Neurology, Bryan Alzheimer's Disease Research Center, and Center for Genomic and Computational Biology, Duke University Medical Center, Durham, North Carolina, USA
34. Dr. Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway
35. Human Longevity Inc, Durham, North Carolina, USA
36. Neuropsychiatric Genetics Research Group, Department of Psychiatry and Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
37. Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
38. Department of Psychology, University of Edinburgh, Edinburgh, UK
39. Division of Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, New York, USA
40. Department of Psychiatry, Hofstra Northwell School of Medicine, Hempstead, New York, USA
41. Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research, Manhasset, New York, USA
42. Clinical and Translational Neuroscience Branch, Intramural Research Program, National Institute of Mental Health, National Institute of Health, Bethesda, Maryland, USA
43. Department of Medical Genetics, Oslo University Hospital, University of Bergen, Oslo, Norway
44. NORMENT, K.G. Jebsen Centre for Psychosis Research, University of Bergen, Bergen, Norway
45. Neuroimaging, Cognition & Genomics (NICOG) Centre, School of Psychology and Discipline of Biochemistry, National University of Ireland, Galway, Ireland
46. 23andMe, Inc., Mountain View, California, USA
47. Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland
48. Helsinki University Hospital, Helsinki, Finland
49. Department of Psychology, University of Oslo, Oslo, Norway
50. Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
51. Department of Psychology, University of Crete, Greece
52. Department of Psychiatry, Martin Luther University of Halle-Wittenberg, Halle, Germany
53. Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA
54. Laboratory of NeuroGenetics, Department of Psychology & Neuroscience, Duke University, Durham, North Carolina, USA
55. Department of Psychiatry, National and Kapodistrian University of Athens Medical School, Eginition Hospital, Athens, Greece
56. University Mental Health Research Institute, Athens, Greece
57. Neurobiology Research Institute, Theodor-Theohari Cozzika Foundation, Athens, Greece

58. Institute for Behavioral Genetics, University of Colorado, Boulder, Colorado, USA
59. Psychiatry and Behavioral Sciences, Division of Medical Psychology, and Department of Neurology, Duke University Medical Center, Durham, North Carolina, USA
60. Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland
61. Helsinki Collegium for Advanced Studies, University of Helsinki, Helsinki, Finland
62. Department of Psychiatry and Biobehavioral Sciences and Department of Molecular and Medical Pharmacology, University of California Los Angeles, Los Angeles, California, USA
63. Department of Biological and Medical Psychology, University of Bergen, Norway
64. K.G. Jebsen Center for Research on Neuropsychiatric Disorders, University of Bergen, Norway
65. Division of Brain Sciences, Department of Medicine, Imperial College, London, UK
66. Centre for Integrated Genomic Medical Research, Institute of Population Health, University of Manchester, Manchester, UK
67. Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland
68. Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Cambridge, UK
69. Massachusetts General Hospital, Center for Human Genetic Research, Psychiatric and Neurodevelopmental Genetics Unit, Boston, Massachusetts, USA
70. Centre for Epidemiology, Division of Population Health, Health Services Research & Primary Care, The University of Manchester, Manchester, UK
71. Division of Neuroscience and Experimental Psychology/ School of Biological Sciences, Faculty of Biology Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Manchester, UK
72. Department of Psychology, Stanford University, Palo Alto, California, USA
73. Institute of Behavioural Sciences, University of Helsinki, Helsinki, Finland
74. Department of Genetics and Genomic Science and Institute for Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, New York, USA
75. Robert and Beverly Lewis Center for Neuroimaging, University of Oregon, Eugene, Oregon, USA
76. NORMENT, K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo and Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
77. Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, UK
78. Lieber Institute for Brain Development, Johns Hopkins University Medical Campus, Baltimore, Maryland, USA
79. Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands
80. Campbell Family Mental Health Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada
81. Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA
82. Center for Statistical Genetics, University of Michigan, Ann Arbor, Michigan, USA
83. Institute of Clinical Medicine, University of Oslo, Oslo, Norway
84. Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, USA
85. College Behavioral and Emotional Health Institute, Virginia Commonwealth University, Richmond, Virginia, USA
86. Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA
87. Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
88. Department of Genetics, University of North Carolina, Chapel Hill, North Carolina, USA
89. Centre for Advanced Imaging, University of Queensland, Brisbane, Australia

These authors contributed equally

*Correspondence to: Danielle Posthuma: Department of Complex Trait Genetics, Vrije Universiteit Amsterdam, De Boelelaan 1085, 1081 HV, Amsterdam, The Netherlands. Phone: +31 20 598 2823, Fax: +31 20 5986926, d.posthuma@vu.nl

Word count: Introductory paragraph: 180; main text: 1519; Online methods: 3,256

Display items: 4 (1 Table, 3 Figures)

Includes **Supplementary Note, Supplementary Figures 1-12, Supplementary Tables 1-26**

Intelligence is highly heritable¹ and a major determinant of human health and well-being². Recent genome-wide meta-analyses have identified 24 genomic loci linked to variation in intelligence³⁻⁷, but much about its genetic underpinnings remains to be discovered. Here, we present the largest genetic association study of intelligence to date (N=269,867), identifying 205 associated genomic loci (190 novel) and 1,016 genes (939 novel) via positional mapping, expression quantitative trait locus (eQTL) mapping, chromatin interaction mapping, and gene-based association analysis. We find enrichment of genetic effects in conserved and coding regions and associations with 146 nonsynonymous exonic variants. Associated genes are strongly expressed in the brain, specifically in striatal medium spiny neurons and hippocampal pyramidal neurons. Gene-set analyses implicate pathways related to nervous system development and synaptic structure. We confirm previous strong genetic correlations with multiple health-related outcomes, and Mendelian randomization results suggest protective effects of intelligence for Alzheimer's disease and ADHD, and bidirectional causation with pleiotropic effects for schizophrenia. These results are a major step forward in understanding the neurobiology of cognitive function as well as genetically related neurological and psychiatric disorders.

We performed a genome-wide association (GWAS) meta-analysis of 14 independent epidemiological cohorts of European ancestry and 9,295,118 genetic variants passing quality control (**Table 1; Supplementary Table 1; Supplementary Figure 1**). A flowchart of the study methodology is presented in **Supplementary Figure 2** and additional details of the methods and results are presented in the **Supplementary Note**.

Intelligence was assessed using various neurocognitive tests, primarily gauging fluid domains of cognitive functioning (**Supplementary Information 1.1-1.2**). Despite variation in form and content, cognitive test scores display a positive manifold of correlations, a robust empirical phenomenon that is observed in multiple populations⁸. Statistically, the variance common across cognitive tasks can be modeled as a latent factor denoted as g (the general factor of intelligence)^{9,10}. In addition, twin- and family studies show strong genetic correlations across diverse cognitive domains¹¹, suggesting pleiotropy, and across levels of ability¹¹, substantiating the view of general intelligence as an aetiological continuum (with rare syndromic forms of severe intellectual disability being the exception¹²). Additionally, g -factors extracted from different sets of cognitive tests correlate very strongly ($>.98^{13,14}$), supporting the universality of $g^{15,16}$. In meta-analyzing cognitive scores obtained using a variety of tests, we aim to boost the statistical power to detect genetic variants underlying g , which are likely to have pleiotropic effects across multiple domains of cognitive functioning.

Despite sample and methodological variations, genetic correlations (r_g) between cohorts were considerable (mean=0.67), and there was no evidence of heterogeneity between cohorts in the single nucleotide polymorphism (SNP) associations (**Supplementary Table 2; Supplementary Results 2.1**). Age-stratified meta-analyses indicated high genetic correlations ($r_g>0.62$), and comparable heritability across age, as captured by the SNPs included in the analysis ($h^2_{SNP}=0.19-0.22$) (**Supplementary Table 3; Supplementary Results 2.2**). The full sample h^2_{SNP} was 0.19 (SE=0.01), in line with previous findings^{4,5}, and an LD score intercept¹⁷ of 1.08 (SE=0.02) indicated that most of the inflation ($\lambda_{GC}=1.92$) could be explained by polygenic signal⁶ (**Supplementary Table 4; Supplementary Figure 3**).

In the meta-analysis, 12,110 variants indexed by 242 lead SNPs in approximate linkage equilibrium ($r^2 < 0.1$) reached genome-wide significance (GWS; $P < 5 \times 10^{-8}$) (**Figure 1a; Supplementary Tables 5-7; Supplementary Figures 4-5**). These were located in 205 distinct genomic loci (**Supplementary Results 2.3.1**). We tested for replication using the proxy phenotype of educational attainment, which is correlated phenotypically ($r \sim 0.40$)¹⁸ and genetically ($r \sim 0.70$)¹⁹ with intelligence. We confirmed this high genetic correlation ($r_g = 0.73$) and observed sign concordance with educational attainment for 93% of GWS SNPs ($P < 1 \times 10^{-300}$), with replication for 48 loci (**Supplementary Results 2.3.2; Supplementary Table 8**). Using polygenic score prediction^{20,21}, the current results explain up to 5.2% of the variance in intelligence in four independent samples (**Supplementary Table 9, Supplementary Results 2.3.3**).

We observed enrichment for heritability of SNPs in conserved regions ($P = 2.01 \times 10^{-12}$), coding regions ($P = 1.67 \times 10^{-6}$), and H3K9ac histone regions/peaks ($P < 6.26 \times 10^{-5}$), and among common (minor allele frequency > 0.3) variants (**Figure 1b; Supplementary Results 2.3.4; Supplementary Table 10; Supplementary Figures 6-7**). Conserved and regulatory regions have previously been implicated in cognitive functioning²² but coding regions have not.

Functional annotation of all candidate SNPs in the associated loci (SNPs with an $r^2 \geq 0.6$ with one of the independent significant SNPs, a suggestive P -value ($P < 1 \times 10^{-5}$) and a $MAF > 0.0001$; $n = 21,368$) showed that these were mostly intronic/intergenic (**Supplementary Table 6; Figure 1**), yet 146 (81 GWS) SNPs were exonic non-synonymous (ExNS) (**Supplementary Table 11, Supplementary Results 2.3.5**). Convergent evidence of strong association ($Z = 9.49$) and

the highest observed probability of a deleterious protein effect (CADD²³ score=34) was found for rs13107325. This missense mutation (MAF=0.065, $P=2.23 \times 10^{-21}$) in *SLC39A8* was the lead SNP in locus 71 and the ancestral allele C was associated with higher scores on intelligence measures. The effect sizes for ExNS were individually small, with each effect allele accounting for a difference of 0.01 to 0.08 standard deviations. **Supplementary Tables 6 and 11** and **Supplementary Results 2.3.5** present a detailed catalog of variants in the associated genomic loci.

To link the associated variants to genes, we applied three gene-mapping strategies implemented in FUMA²⁴. *Positional* gene-mapping aligned SNPs to 522 genes by genomic location, *eQTL (expression quantitative trait loci)* gene-mapping matched cis-eQTL SNPs to 684 genes whose expression levels they influence, and *chromatin interaction* mapping annotated SNPs to 227 genes based on three-dimensional DNA-DNA interactions (**Figure 2; Supplementary Results 2.3.6; Supplementary Figures 8-9; Supplementary Tables 12-14**). This resulted in 859 unique mapped genes, 435 of which were implicated by at least two mapping strategies and 139 by all three (**Figure 3**). Although not all of these genes are certain to have a role in intelligence, they point to potential functional links for the GWAS associated variants and give higher credibility to genes with convergent evidence of association from multiple sources. The FUMA-mapped genes were enriched for brain tissue expression and several regulatory biological gene-sets (**Supplementary Results 2.3.6**). Fifteen genes are particularly notable as they are implicated via chromatin interactions between two independent genomic risk loci (**Figure 2; Supplementary Results 2.3.6**). Cross-locus interactions implicated *ELAVL2*, *PTCH1*, *ATF4*, *FBXL17*, and *MAN2A1* in left ventricle of the heart tissue, *SATB2* in liver tissue, and *MEF2C* in 5 tissues. Multiple interactions in multiple

tissue types were seen for a cluster of 8 genes on chromosome 6 encoding zinc finger proteins and histones.

We performed genome-wide gene-based association analysis (GWGAS) using MAGMA²⁵ to estimate aggregate associations based on all SNPs in a gene (whereas FUMA annotates individually significant SNPs to genes). GWGAS identified 507 associated genes (**Figure 3a; Supplementary Results 2.4.1; Supplementary Table 15**), of which 350 were also mapped by FUMA (**Figure 3b**). In total, 105 genes were implicated by all four strategies (**Supplementary Table 16**).

In gene-set analysis, six Gene Ontology²⁶ gene-sets were significantly associated with intelligence: *neurogenesis* ($P=4.78\times10^{-7}$), *neuron differentiation* ($P=4.82\times10^{-6}$), *central nervous system neuron differentiation* ($P=3.31\times10^{-6}$), *regulation of nervous system development* ($P=9.30\times10^{-7}$), *positive regulation of nervous system development* ($P=1.00\times10^{-6}$), and *regulation of synapse structure or activity* ($P=5.42\times10^{-6}$) (**Supplementary Results 2.4.2; Supplementary Tables 17-18**). Conditional analysis indicated that there were three independent associations, *regulation of nervous system development*, *central nervous system neuron differentiation*, and *regulation of synapse structure or activity*, which together accounted for the associations of the other sets.

Linking gene-based P -values to tissue-specific gene-sets, we observed strong associations with gene expression across multiple brain areas (**Figure 3c; Supplementary Results 2.4.2; Supplementary Table 19**), particularly the frontal cortex ($P=3.10\times10^{-9}$). In brain single-cell expression gene-set analyses, we found significant associations of striatal medium spiny

neurons ($P=2.02\times 10^{-14}$) and pyramidal neurons in the CA1 hippocampal ($P=5.67\times 10^{-11}$) and cortical somatosensory regions ($P=2.72\times 10^{-9}$) (**Figure 3d; Supplementary Results 2.4.2; Supplementary Table 20**). Conditional analysis showed that the independent association signal in brain cells was driven by medium spiny neurons, neuroblasts, and pyramidal CA1 neurons.

Intelligence has been associated with a wide variety of human behaviors¹⁵ and brain anatomy²⁷. Confirming previous reports^{5,6}, we observed negative genetic correlations with ADHD ($r_g=-0.36$, $P=4.58\times 10^{-23}$), depressive symptoms ($r_g=-0.27$, $P=6.20\times 10^{-10}$), Alzheimer's disease ($r_g=-0.27$, $P=2.03\times 10^{-5}$), and schizophrenia ($r_g=-0.21$, $P=3.82\times 10^{-17}$), and positive correlations with longevity ($r_g=0.43$, $P=7.96\times 10^{-8}$) and autism ($r_g=0.25$, $P=3.14\times 10^{-7}$), among others (**Supplementary Table 21; Supplementary Figure 10**). Comparison with previous GWAS²⁸ supported these correlations, showing numerous shared genetic variants across phenotypes (**Supplementary Results 2.5; Supplementary Tables 22-23**). Low enrichment (87 of 1,518 genes, $P=0.05$) was found for genes previously linked to intellectual disability or developmental delay, indicating largely distinct biological processes. However, our results extend previous genetic research on normal variation in general intelligence, as catalogued in **Supplementary Tables 24-25**.

We used Generalized Summary-statistic-based Mendelian Randomization²⁹ to test for potential credible causal associations between intelligence and genetically correlated traits (**Supplementary Results 2.5.3; Supplementary Figures 11-12; Supplementary Table 26**). We observed a strong bidirectional effect of cognitive ability on educational attainment ($b_{xy}=0.549$, $P<1\times 10^{-320}$) and of educational attainment on intelligence ($b_{yx}=0.480$, $P=6.85\times 10^{-}$

⁸²). Such findings are consistent with previous studies implicating bidirectional causal effects^{30,31}. There was also a bidirectional association showing a strong protective effect of intelligence on schizophrenia ($OR=0.50$, $b_{xy}=-0.685$, $P=2.02\times 10^{-57}$) and a relatively smaller reverse effect ($b_{yx}= -0.214$, $P=4.19\times 10^{-52}$), with additional evidence for pleiotropy (**Supplementary Results 2.5.3**). A number of previous reports support both a causal link and genetic overlap between these phenotypes^{32,33}. Our results also suggested that higher intelligence had a protective effect on ADHD ($OR=0.48$, $b_{xy}=-0.734$, $P=2.57\times 10^{-46}$) and Alzheimer's disease ($OR=0.65$, $b_{xy}=-0.435$, $P=3.59\times 10^{-14}$), but was associated with higher risk of autism ($OR=1.38$, $b_{xy}=0.321$, $P=1.12\times 10^{-3}$).

In the present study, we have affirmed and expanded existing knowledge of the genetics of general intelligence, identifying 190 novel loci and 939 novel associated genes and replicating previous associations with 15 loci and 77 genes. The combined strategies of functional annotation and gene-mapping using biological data resources provide extensive information on the likely consequences of relevant genetic variants and put forward a rich set of plausible gene targets and biological mechanisms for functional follow-up. Gene-set analyses contribute novel insight into underlying neurobiological pathways, confirming the importance of brain-expressed genes and neurodevelopmental processes in fluid domains of intelligence and pointing towards the involvement of specific cell types. Our results indicate overlap in the genetic processes involved in both cognitive functioning and neurological and psychiatric traits and provide suggestive evidence of causal associations that may drive these correlations. These results are important for understanding the biological underpinnings of cognitive functioning and contribute to our understanding of related neurological and psychiatric disorders.

URLs:

UK Biobank website: <http://ukbiobank.ac.uk>

UK Biobank genotyping: <http://www.biorxiv.org/content/early/2017/07/20/166298>

Health and Retirement study: <http://hrsonline.isr.umich.edu>

Genes for Good study: <http://genesforgood.org>

International Cognitive Ability Resource measure (Genes for Good): <https://icar-project.com/>

Functional Mapping and Annotation (FUMA) software: <http://fuma.ctglab.nl>

Multi-marker Analysis of GenoMic Annotation (MAGMA) software:
<http://ctg.cncr.nl/software/magma>

METAL software: http://genome.sph.umich.edu/wiki/METAL_Program

LD Score Regression software: <https://github.com/bulik/ldsc>

LD Hub (GWAS summary statistics): <http://ldsc.broadinstitute.org/>

LD scores: <https://data.broadinstitute.org/alkesgroup/LDSCORE/>

GeneCards: <http://www.genecards.org>

Psychiatric Genomics Consortium (GWAS summary statistics):
<http://www.med.unc.edu/pgc/results-and-downloads>

MSigDB curated gene-set database:
<http://software.broadinstitute.org/gsea/msigdb/collections.jsp>

NHGRI GWAS catalog: <https://www.ebi.ac.uk/gwas/>

RegionAnnotator: <https://github.com/ivankosmos/RegionAnnotator>

Generalized Summary-data-based Mendelian Randomization software:
<http://cnsgenomics.com/software/gsmr/>

Acknowledgments

This work was funded by The Netherlands Organization for Scientific Research (NWO VICI 453-14-005 and NWO VIDI 452-12-014 to D.P.) and the Sophia Foundation for Scientific Research (SSWO grant S-1427 to P.R.J.). The analyses were carried out on the Genetic Cluster Computer, which is financed by the Netherlands Scientific Organization (NWO: 480-05-003), Vrije Universiteit, Amsterdam, The Netherlands, and the Dutch Brain Foundation, and is hosted by the Dutch National Computing and Networking Services SurfSARA. Support for data analysis was also provided by the Swiss National Science Foundation (to J.B.). This research has been conducted using the UK Biobank resource under application number 16406. We thank the numerous participants, researchers, and staff from many studies who collected and contributed to the data. Additional acknowledgments can be found in the Supplementary Information file.

Author Contributions

D.P., J.E.S. and P.R.J. performed the analyses. D.P. conceived the idea of the study and supervised analyses. S.St. performed QC on the UK Biobank data and wrote the analysis pipeline. K.W. constructed and applied the FUMA pipeline for performing follow-up analyses. J.B. conducted the single cell enrichment analyses. C.A.d.L., M.Na., A.R.Ham., T.J.C.P., and S.v.d.S. assisted with pipeline development and data analysis. S.A., P.B.B., J.R.I.C., K.L.G., J.A.K., R.K., E.Kr., M.L., M.Ny., C.A.R., J.W.T., H.Y., D.Z., S.H., N.K.H., I.K.K., S.L., G.W.M., A.B.M.-M., E.B.Q., G.S., N.G.S., B.T.W., D.E.A., D.K., D.A., R.M.B., P.B., K.E.B., T.D.C., O.C.-F., A.Ch., E.T.C., E.C., A.Co., G.Da., I.J.D., P.D., D.D., S.D., G.Do., E.D.C., J.G.E., T.E., N.A.F., D.C.G., I.G., M.G., S.G., A.R.Har., A.Ha., M.C.K., E.Kn., B.K., J.L., S.L.-H., T.L., D.C.L., E.L., A.J.L., A.K.M., I.M., D.M., A.C.N., W.O., A.Pal., A.Pay., N.P., R.A.P., K.R., I.R., P.R., D.R., F.W.S., M.A.S., O.B.S., N.S., J.M.S., V.M.S., N.C.S., R.E.S., K.S., A.N.V., D.R.W., E.W., J.Y., G.A., O.A.A., G.B., L.C., B.D., D.M.D., A.He., J.H.-L., M.A.I., K.S.K., N.G.M., S.E.M., N.L.P., R.P., T.J.C.P., S.R., P.F.S., H.T., S.I.V., and M.J.W. contributed data. T.W. read and commented on the paper. D.P., J.E.S. and P.R.J. wrote the paper. All authors critically reviewed the paper.

Competing Financial Interests Statement

PF Sullivan reports the following potentially competing financial interests: Lundbeck (advisory committee), Pfizer (Scientific Advisory Board member), and Roche (grant recipient, speaker reimbursement). G Breen reports consultancy and speaker fees from Eli Lilly and Illumina and grant funding from Eli Lilly. J Hjerling-Leffler reports interests from Cartana (Scientific Advisor) and Roche (grant recipient). TD Cannon is a consultant to Boehringer Ingelheim Pharmaceuticals and Lundbeck A/S. All other authors declare no financial interests or potential conflicts of interest.

References

- 1 Polderman, T. J. *et al.* Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* **47**, 702-709, doi:10.1038/ng.3285 (2015).
- 2 Wraw, C., Deary, I. J., Gale, C. R. & Der, G. Intelligence in youth and health at age 50. *Intelligence* **53**, 23-32, doi:10.1016/j.intell.2015.08.001 (2015).
- 3 Davies, G. *et al.* Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53949). *Mol Psychiatry* **20**, 183-192, doi:10.1038/mp.2014.188 (2015).
- 4 Davies, G. *et al.* Genome-wide association study of cognitive functions and educational attainment in UK Biobank (N=112 151). *Mol Psychiatry* **21**, 758-767, doi:10.1038/mp.2016.45 (2016).
- 5 Sniekers, S. *et al.* Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence. *Nat Genet* **49**, 1107-1112, doi:10.1038/ng.3869 (2017).
- 6 Trampush, J. W. *et al.* GWAS meta-analysis reveals novel loci and genetic correlates for general cognitive function: a report from the COGENT consortium. *Mol Psychiatry* **22**, 336-345, doi:10.1038/mp.2016.244 (2017).
- 7 Zabaneh, D. *et al.* A genome-wide association study for extremely high intelligence. *Mol Psychiatry*, doi:10.1038/mp.2017.121 (2017).
- 8 Jensen, A. R. *The G Factor: The Science of Mental Ability.* (Praeger, 1998).
- 9 Carroll, J. B. *Human Cognitive Abilities: A Survey of Factor-Analytic Studies.* (Cambridge University Press, 1993).
- 10 Spearman, C. "General Intelligence," Objectively Determined and Measured. *The American Journal of Psychology* **15**, 201-292, doi:10.2307/1412107 (1904).
- 11 Plomin, R. & Kovas, Y. Generalist genes and learning disabilities. *Psychol Bull* **131**, 592-617, doi:10.1037/0033-2909.131.4.592 (2005).
- 12 Plomin, R. & von Stumm, S. The new genetics of intelligence. *Nat Rev Genet*, doi:10.1038/nrg.2017.104 (2018).
- 13 Johnson, W., Bouchard, T. J., Krueger, R. F., McGue, M. & Gottesman, I. I. Just one g: consistent results from three test batteries. *Intelligence* **32**, 95-107, doi:https://doi.org/10.1016/S0160-2896(03)00062-X (2004).
- 14 Johnson, W., Nijenhuis, J. t. & Bouchard, T. J. Still just 1 g: Consistent results from five test batteries. *Intelligence* **36**, 81-95, doi:https://doi.org/10.1016/j.intell.2007.06.001 (2008).
- 15 Deary, I. J., Penke, L. & Johnson, W. The neuroscience of human intelligence differences. *Nat Rev Neurosci* **11**, 201-211, doi:10.1038/nrn2793 (2010).
- 16 Deary, I. J. Intelligence. *Annu Rev Psychol* **63**, 453-482, doi:10.1146/annurev-psych-120710-100353 (2012).
- 17 Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* **47**, 291-295, doi:10.1038/ng.3211 (2015).
- 18 Deary, I. J., Strand, S., Smith, P. & Fernandes, C. Intelligence and educational achievement. *Intelligence* **35**, 13-21, doi:https://doi.org/10.1016/j.intell.2006.02.001 (2007).

- 19 Rietveld, C. A. *et al.* GWAS of 126,559 individuals identifies genetic variants associated with educational attainment. *Science* **340**, 1467-1471, doi:10.1126/science.1235488 (2013).
- 20 Euesden, J., Lewis, C. M. & O'Reilly, P. F. PRSice: Polygenic Risk Score software. *Bioinformatics* **31**, 1466-1468, doi:10.1093/bioinformatics/btu848 (2015).
- 21 Vilhjalmsdottir, B. J. *et al.* Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet* **97**, 576-592, doi:10.1016/j.ajhg.2015.09.001 (2015).
- 22 Hill, W. D. *et al.* Molecular genetic aetiology of general cognitive function is enriched in evolutionarily conserved regions. *Transl Psychiatry* **6**, e980, doi:10.1038/tp.2016.246 (2016).
- 23 Kircher, M. *et al.* A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet* **46**, 310-315, doi:10.1038/ng.2892 (2014).
- 24 Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. FUMA: Functional mapping and annotation of genetic associations. *Nat Commun* **8**, 1826. doi:10.1038/s41467-017-01261-5 (2017).
- 25 de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput Biol* **11**, e1004219, doi:10.1371/journal.pcbi.1004219 (2015).
- 26 Ashburner, M. *et al.* Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. *Nat Genet* **25**, 25-29, doi:10.1038/75556 (2000).
- 27 Posthuma, D. *et al.* The association between brain volume and intelligence is of genetic origin. *Nat Neurosci* **5**, 83-84, doi:10.1038/nn0202-83 (2002).
- 28 MacArthur, J. *et al.* The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Res* **45**, D896-d901, doi:10.1093/nar/gkw1133 (2017).
- 29 Zhu, Z. *et al.* Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat Commun* **9**, 224, doi: 10.1038/s41467-017-02317-2 (2018).
- 30 Johnson, W., Deary, I. J. & Iacono, W. G. Genetic and environmental transactions underlying educational attainment. *Intelligence* **37**, 466-478, doi:https://doi.org/10.1016/j.intell.2009.05.006 (2009).
- 31 Richards, M. & Sacker, A. Is education causal? Yes. *Int J Epidemiol* **40**, 516-518, doi:10.1093/ije/dyq166 (2011).
- 32 Kendler, K. S., Ohlsson, H., Sundquist, J. & Sundquist, K. IQ and Schizophrenia in a Swedish National Sample: Their Causal Relationship and the Interaction of IQ with Genetic Risk. *Am J Psychiatry* **172**, 259-265, doi:10.1176/appi.ajp.2014.14040516 (2015).
- 33 Le Hellard, S. *et al.* Identification of Gene Loci That Overlap Between Schizophrenia and Educational Attainment. *Schizophr Bull* **43**, 654-664 (2017).

Figure Legends

Figure 1. SNP-based associations with intelligence in the GWAS meta-analysis of N=269,867 independent individuals. (a) Manhattan plot showing the $-\log_{10}$ transformed two-tailed P -value of each SNP from the GWAS meta-analysis (of linear and logistic regression statistics) on the y-axis and base pair positions along the chromosomes on the x-axis. The dotted red line indicates Bonferroni-corrected genome-wide significance ($P < 5 \times 10^{-8}$); the blue line the threshold for suggestive associations ($P < 1 \times 10^{-5}$). Independent lead SNPs are indicated by a diamond. (b) Heritability enrichment of 28 functional annotation categories for SNPs in the meta-analysis, calculated with stratified LD score regression. Error bars show 95% confidence intervals around the enrichment estimate. The dashed horizontal line indicates no enrichment of the annotation category. Red dots indicate significant Bonferroni-corrected two-tailed P -values and beige dots indicate suggestive ($P < .05$) values. UTR=untranslated region; TSS=transcription start site; CTCF=CCCTC-binding factor; DHS=DNaseI Hypersensitive Site; TFBS=transcription factor binding site; DGF=DNaseI digital genomic footprint. (c) Distribution of functional consequences of SNPs in genomic risk loci in the meta-analysis. (d) Distribution of RegulomeDB score for SNPs in genomic risk loci, with a low score indicating a higher likelihood of having a regulatory function (**Online methods**). (e) The minimum chromatin state across 127 tissue and cell types for SNPs in genomic risk loci, with lower states indicating higher accessibility and states 1-7 referring to open chromatin states (**Online Methods**).

Figure 2. Cross-locus interactions for genomic regions associated with intelligence in 269,867 independent individuals. Circos plots showing genes on chromosomes 2 (a), 5 (b), 6 (c), 9 (d), and 22 (e) that were linked to genomic risk loci in the GWAS meta-analysis (blue regions) by eQTL mapping (green lines connecting an eQTL SNP to its associated gene), and/or chromatin interactions (orange lines connecting two interacting regions) and showed evidence of interaction across two independent genomic risk loci. Genes implicated by eQTL are in green, by chromatin interactions in orange, and by both eQTL and chromatin interactions mapping in red. The outer layer shows a Manhattan plot containing the $-\log_{10}$ transformed two-tailed P -value of each SNP from the GWAS meta-analysis (of linear and logistic regression statistics), with genome-wide significant SNPs colored according to linkage disequilibrium patterns with the lead SNP. Circos plots for all chromosomes are provided in **Supplementary Fig. 8**.

Figure 3. Implicated genes, pathways, and tissue- and cell- expression profiles for intelligence in 269,867 independent individuals. (a) Manhattan plot of the genome-wide gene-based association analysis (GWGAS). The y-axis shows the $-\log_{10}$ transformed two-tailed P -value of each gene from a linear model, and the chromosomal position on the x-axis. The red dotted line indicates the Bonferroni-corrected threshold for genome-wide significance of the gene-based test ($P < 2.76 \times 10^{-6}$; $0.05/18,128$ genes), and the blue line indicates the suggestive threshold ($P < 2.76 \times 10^{-5}$; $0.5/18,128$ genes) (b) Venn diagram showing overlap of genes implicated by positional mapping, eQTL mapping, chromatin interaction mapping, and GWGAS. (c) Gene expression profiles of associated genes in 53 tissue types. The y-axis shows the $-\log_{10}$ transformed two-tailed P -value of association of GWGAS test statistics with tissue-specific gene expression levels in a linear model. Expression data were extracted from the Genotype-Tissue Expression (GTEx) database. Expression values (RPKM)

were log2 transformed with pseudocount 1 after winsorization at 50 and averaged per tissue. The dotted blue line indicates the Bonferroni-corrected significance threshold ($P=0.05/7,323$ gene-sets= 6.83×10^{-6}). **(d)** Single-cell gene-expression analysis of genes related to intelligence in 24 cell-types. The x-axis shows the $-\log_{10}$ transformed two-tailed P -value of association of GWAS test statistics with cell-specific gene expression levels in a linear model. The dotted blue line indicates the Bonferroni-corrected significance threshold ($P=0.05/7,323$ gene-sets= 6.83×10^{-6}).

Tables

Table 1. Overview of cohorts included in a GWAS meta-analysis of general intelligence.

Cohort	N	Age	Phenotype
1. UKB	195,653	39-72	Verbal and mathematical reasoning
2. COGENT	35,289	8-96	One or more neuropsychological tests from three or more domains of cognitive performance
3. RS	6,182	45-98	Letter-digit substitution, Stroop, verbal fluency, delayed recall
4. GENR	1,929	5-9	SON-R (spatial visualization and abstract reasoning subsets)
5. STR	3,215	18	Logical, verbal, spatial, and technical ability subtests
6. S4S	2,818	17-18	SAT test scores
7. HiQ / HRS	9,410	*	High IQ cases / unselected population controls
8. TEDS	3,414	12	WISC-III verbal and nonverbal reasoning; Raven's progressive matrices
9a. DTR - MADT	737	55-80	Verbal fluency, digit span, immediate and delayed recall tests
9b. DTR - LSADT	253	73-94	Verbal fluency, digit span, immediate and delayed recall tests
10. IMAGEN	1,343	14	WISC-IV, CANTAB factor score
11a. BLTS - Children	530	12-13	VSRT-C factor score
11b. BLTS - Adolescents	2,598	15-30	MAB-II IQ score
12. NESCOG	252	18-79	WAIS IQ score
13. GfG	5,084	15-91	ICAR verbal reasoning test
14a. STSA - SATSA+GENDER	703	50-94	Verbal, spatial, episodic memory, and processing speed tests
14b. STSA - HARMONY	448	65-96	Verbal, spatial, episodic memory, and processing speed tests

* HiQ/HRS sample used a case-control design rather than a cognitive test score ascertained at a specific age; see **Online Methods** and **Supplementary information 1.1**.

Online Methods

Study Cohorts

The meta-analysis included new and previously reported GWAS summary statistics from 14 cohorts: UK Biobank (UKB), Cognitive Genomics Consortium (COGENT), Rotterdam Study (RS), Generation R Study (GENR), Swedish Twin Registry (STR), Spit for Science (S4S), High-IQ/Health and Retirement Study (HiQ/HRS), Twins Early Development Study (TEDS), Danish Twin Registry (DTR), IMAGEN, Brisbane Longitudinal Twin Study (BLTS), Netherlands Study of Cognition, Environment and Genes (NESCOG), Genes for Good (GfG), and the Swedish Twin Studies of Aging (STSA). All samples were obtained from epidemiological cohorts ascertained for research on a variety of physical and psychological outcomes. Participants ranged from children to older adults, with older samples being screened for cognitive decline to exclude the possibility of dementia affecting performance on cognitive tests.

Different measures of intelligence were assessed in each cohort but were all operationalized to index a common latent g factor underlying multiple dimensions of cognitive functioning. With the exception of HiQ/HRS, all cohorts extracted a single sum score, mean score, or factor score from a multidimensional set of cognitive performance tests and used this normally-distributed score as the phenotype in a covariate-adjusted (e.g. age, sex, ancestry principal components) GWAS using linear regression methods. For HiQ/HRS, a logistic regression GWAS was run with “case” status reflecting whether participants were drawn from an extreme-sampled population of very high intelligence (i.e. at the upper ~0.03% of the tail of the normal distribution) versus an epidemiological sample of unselected population “controls”. Detailed descriptions of the samples, measures, genotyping, quality control, and analysis procedures for each cohort are provided in the **Supplementary Note (Supplementary Information 1.1-1.2)**, **Supplementary Table 1**, and in the **Life Sciences Reporting Summary**.

Meta-analysis

Stringent quality control measures were applied to the summary statistics for each GWAS cohort before combining. All files were checked for data integrity and accuracy. SNPs were filtered from further analysis if they met any of the following criteria: imputation quality (INFO/R²) score < 0.6, Hardy-Weinberg equilibrium (HWE) $P < 5 \times 10^{-6}$, study-specific minor allele frequency (MAF) corresponding to a minor allele count (MAC) < 100, and mismatch of alleles or allele frequency difference greater than 20% from the Haplotype Reference Consortium (HRC) genome reference panel¹⁶. Some cohorts used more stringent criteria (see **Supplementary Information 1.1**). Indels and SNPs that were duplicated, multi-allelic, monomorphic, or ambiguous (A/T or C/G with a MAF >0.4) were also excluded. Visual inspection of the distribution of the summary statistics was completed, and Manhattan plots and QQ plots were created for the cleaned summary statistics from each cohort (**Supplementary Figure 1**).

The SNP association P -values from the GWAS cohorts were meta-analyzed with METAL³⁴ (see **URLs**) in two phases. First, we meta-analyzed all cohorts with quantitative phenotypes (all except HiQ/HRS) using a sample-size weighted scheme. In the second phase, we added the HiQ/HRS study results to the first phase results, weighting each set of summary statistics by their respective non-centrality parameter (NCP). This method improves power when using an extreme case sampling design such as HiQ³⁵ and provides a comparable metric with which to combine information from different analytic designs while accounting for their differences in power/effective sample size. NCPs were estimated using the Genetic Power Calculator³⁶, as described by Coleman et al.³⁷. After combining all data, meta-analysis results were further filtered to exclude any variants with $N < 50,000$. We additionally included a random-effects

meta-analysis for each phase, as implemented in METAL, to evaluate potential heterogeneity in the SNP association statistics between cohorts.

The X chromosome was treated separately in the meta-analysis because imputed genotypes were not available for the X chromosome in the largest cohort (UKB), and there was little overlap between the UKB called genotypes and imputed data from other cohorts ($N_{\text{SNPs}} < 500$). We therefore included only the called X chromosome variants in UKB for these analyses after performing X-specific quality control steps³⁸.

We conducted a series of meta-analyses on subsets of the full sample using the same methods as above. Age group-specific meta-analyses were run in the cohorts of children (age < 17; GENR, TEDS, IMAGEN, BLTS; N=9,814), young adults (age ~17-18; S4S, STR; N=6,033), adults (age > 18, primarily middle-aged or older: UKB, RS, DTR, NESCOG, STSA; N=204,228), and older adults (mean age > 60, RS, DTR, STSA; N=8,323), excluding studies whose samples overlapped child/young adult and adult groups (COGENT, HiQ/HRS, GfG; N=49,792). To create independent discovery samples for use in polygenic score validation, we also conducted meta-analyses with a “leave-one-out” strategy in which summary statistics from four validation datasets were, respectively, excluded from the meta-analysis (see *Polygenic Scoring*, below).

Cohort Heritability and Genetic Correlation

LD score regression¹⁷ was used to estimate genomic inflation and heritability of the intelligence phenotypes in each of the 14 cohorts using their post-quality control summary statistics, and to estimate the cross-cohort genetic correlations³⁹. Pre-calculated LD scores from the 1000 Genomes European reference population were obtained online ([see URLs](#)). Genetic correlations were calculated on HapMap3 SNPs only. LD score regression was also

used on the age subgroup meta-analyses to estimate heritability and cross-age genetic correlations.

Genomic Risk Loci Definition

Independently associated loci from the meta-analysis were defined using FUMA²⁴ ([see URLs](#)), an online platform for functional mapping of genetic variants. We first identified *independent significant SNPs* which had a Bonferroni-corrected genome-wide significant two-tailed P -value ($P < 5 \times 10^{-8}$) and represented signals that were independent from each other at $r^2 < 0.6$. These SNPs were further represented by *lead SNPs*, which are a subset of the independent significant SNPs that are in approximate linkage equilibrium with each other at $r^2 < 0.1$. We then defined associated *genomic loci* by merging any physically overlapping lead SNPs (linkage disequilibrium [LD] blocks <250kb apart). Borders of the associated genomic loci were defined by identifying all SNPs in LD ($r^2 \geq 0.6$) with one of the independent significant SNPs in the locus, and the region containing all of these *candidate SNPs* was considered to be a single independent genomic locus. All LD information was calculated from UK Biobank genotype data.

Proxy-replication with Educational Attainment

We conducted GWAS of educational attainment, an outcome with a high genetic correlation with intelligence⁵, in a non-overlapping European subset of the UKB sample (N=188,435) who did not complete the intelligence measure. Educational attainment was coded as maximum years of education completed, using the same methods as earlier analyses⁴⁰ and GWAS was conducted using the same quality control and analytic procedures as described for the UKB intelligence phenotype (**Supplementary Information 1.1.1**). To test replication of the SNPs

with this proxy phenotype, we performed a sign concordance test for all GWS SNPs from the meta-analysis using the two-tailed exact binomial test. For each independent genomic locus, we considered it to be evidence for replication if the lead SNP or another correlated SNP in the region was sign concordant with the corresponding SNP in the intelligence meta-analysis and had a two-tailed P -value of association with educational attainment smaller than $0.05/242$ independent tests = 0.0002.

Polygenic Scoring

We calculated polygenic scores (PGS) based on the SNP effect sizes of the leave-one-out meta-analyses, from which four cohorts were (separately) excluded and reserved for score validation. These included a child (GENR), young adult (S4S), and adult sample (RS). We also included the UKB-wb sample to test for validation in a very large ($N = 53,576$) cohort with the greatest phenotypic similarity to the largest contributor to the meta-analysis statistics (UKB-ts), in order to maximize potential predictive power. PGS were calculated on the genotype data using LDpred²¹, a Bayesian PGS method that utilizes a prior on effect size distribution to remodel the SNP effect size and account for LD, and PRSice²⁰, a PLINK⁴¹-based program that automates optimization of the set of SNPs included in the PGS based on a high-resolution filtering of the GWAS P -value threshold. LDpred PGS were applied to the called, cleaned, genotyped variants in each of the validation cohorts with UK Biobank as the LD reference panel. PRSice PGS were calculated on hard-called imputed genotypes using P -value thresholds from 0.0 to 0.5 in steps of 0.001. The explained variance (ΔR^2) was derived from a linear model in which the GWAS intelligence phenotype was regressed on each PGS while controlling for the same covariates as in each cohort-specific GWAS, compared to a linear model with GWAS covariates only.

Stratified Heritability

We partitioned SNP heritability using stratified LD Score regression⁴² in three ways: 1) by functional annotation category, 2) by minor allele frequency (MAF) in six percentile bins, and 3) by chromosome. Annotations for 28 binary categories of putative functional genomic characteristics (e.g. coding or regulatory regions) were obtained from the LD score website ([see URLs](#)). With this method, enrichment/depletion of heritability in each category is calculated as the proportion of heritability attributable to SNPs in the specified category divided by the proportion of total SNPs annotated to that category. The Bonferroni-corrected significance threshold was $.05/56 \text{ annotations} = .0009$.

Functional Annotation of SNPs

Functional annotation of SNPs implicated in the meta-analysis was performed using FUMA²⁴ ([see URLs](#)). We selected all *candidate SNPs* in associated genomic loci having an $r^2 \geq 0.6$ with one of the independent significant SNPs (see above), a suggestive P -value ($P < 1e-5$) and a $MAF > 0.0001$ for annotations. Predicted functional consequences for these SNPs were obtained by matching SNPs' chromosome, base-pair position, and reference and alternate alleles to databases containing known functional annotations, including ANNOVAR⁴³ categories, Combined Annotation Dependent Depletion (CADD) scores²³, RegulomeDB⁴⁴ (RDB) scores, and chromatin states^{45,46}. ANNOVAR categories identify the SNP's genic position (e.g. intron, exon, intergenic) and associated function. CADD scores predict how deleterious the effect of a SNP is likely to be for a protein structure/function, with higher scores referring to higher deleteriousness. A CADD score above 12.37 is the threshold to be potentially pathogenic²³. The RegulomeDB score is a categorical score based on information from

expression quantitative trait loci (eQTLs) and chromatin marks, ranging from 1a to 7 with lower scores indicating an increased likelihood of having a regulatory function. Scores are as follows: 1a=eQTL + Transcription Factor (TF) binding + matched TF motif + matched DNase Footprint + DNase peak; 1b=eQTL + TF binding + any motif + DNase Footprint + DNase peak; 1c=eQTL + TF binding + matched TF motif + DNase peak; 1d=eQTL + TF binding + any motif + DNase peak; 1e=eQTL + TF binding + matched TF motif; 1f=eQTL + TF binding / DNase peak; 2a=TF binding + matched TF motif + matched DNase Footprint + DNase peak; 2b=TF binding + any motif + DNase Footprint + DNase peak; 2c=TF binding + matched TF motif + DNase peak; 3a=TF binding + any motif + DNase peak; 3b=TF binding + matched TF motif; 4=TF binding + DNase peak; 5=TF binding or DNase peak; 6=other; 7=Not available. The chromatin state represents the accessibility of genomic regions (every 200bp) with 15 categorical states predicted by a hidden Markov model based on 5 chromatin marks for 127 epigenomes in the Roadmap Epigenomics Project⁴⁶. A lower state indicates higher accessibility, with states 1-7 referring to open chromatin states. We annotated the minimum chromatin state across tissues to SNPs. The 15-core chromatin states as suggested by Roadmap are as follows: 1=Active Transcription Start Site (TSS); 2=Flanking Active TSS; 3=Transcription at gene 5' and 3'; 4=Strong transcription; 5= Weak Transcription; 6=Genic enhancers; 7=Enhancers; 8=Zinc finger genes & repeats; 9=Heterochromatic; 10=Bivalent/Poised TSS; 11=Flanking Bivalent/Poised TSS/Enhancer; 12=Bivalent Enhancer; 13=Repressed PolyComb; 14=Weak Repressed PolyComb; 15=Quiescent/Low. Standardized SNP effect sizes were calculated for the most impactful SNPs by transforming the sample size-weighted meta-analysis Z score, as described by Zhu et al.⁴⁷.

Gene-mapping

Genome-wide significant loci obtained by the GWAS meta-analysis were mapped to genes in FUMA²⁴ using three strategies:

1. Positional mapping maps SNPs to genes based on physical distance (within a 10kb window) from known protein coding genes in the human reference assembly (GRCh37/hg19).
2. eQTL mapping maps SNPs to genes with which they show a significant eQTL association (i.e. allelic variation at the SNP is associated with the expression level of that gene). eQTL mapping uses information from 45 tissue types in 3 data repositories (GTEx⁴⁸, Blood eQTL browser⁴⁹, BIOS QTL browser⁵⁰), and is based on cis-eQTLs which can map SNPs to genes up to 1Mb apart. We used a false discovery rate (FDR) of 0.05 to define significant eQTL associations.
3. Chromatin interaction mapping was performed to map SNPs to genes when there is a three-dimensional DNA-DNA interaction between the SNP region and a gene region. Chromatin interaction mapping can involve long-range interactions as it does not have a distance boundary. FUMA currently contains Hi-C data of 14 tissue types from the study of Schmitt et al⁵¹. Since chromatin interactions are often defined in a certain resolution, such as 40kb, an interacting region can span multiple genes. If a SNPs is located in a region that interacts with a region containing multiple genes, it will be mapped to each of those genes. To further prioritize candidate genes, we selected only interaction-mapped genes in which one region involved in the interaction overlaps with a predicted enhancer region in any of the 111 tissue/cell types from the Roadmap Epigenomics Project⁴⁶ and the other region is located in a gene promoter region (250bp up and 500bp downstream of the transcription start site and also

predicted by Roadmap to be a promoter region). This reduces the number of genes mapped but increases the likelihood that those identified will have a plausible biological function. We used a FDR of 1×10^{-5} to define significant interactions, based on previous recommendations⁵¹ modified to account for the differences in cell lines used here.

Functional annotation of mapped genes

Genes implicated by mapping of significant GWAS SNPs were further investigated using the GENE2FUNC procedure in FUMA²⁴, which provides hypergeometric tests of enrichment of the list of mapped genes in 53 GTEx⁴⁸ tissue-specific gene expression sets, 7,246 MSigDB gene-sets⁵², and 2,195 GWAS catalog gene-sets²⁸. The Bonferroni-corrected significance threshold was $0.05/9,494 \text{ gene-sets} = 5.27 \times 10^{-6}$.

Gene-based analysis

SNP-based *P*-values from the meta-analysis were used as input for the gene-based genome-wide association analysis (GWGAS). 18,128 protein-coding genes (each containing at least 1 GWAS SNP) from the NCBI 37.3 gene definitions were used as basis for GWGAS in MAGMA²⁵ ([see URLs](#)). The Bonferroni-corrected genome-wide significance threshold was $.05/18,128 \text{ genes} = 2.76 \times 10^{-6}$.

Gene-set analysis

Results from the GWGAS analyses were used to test for association in three types of predefined gene-sets:

1. 7,246 curated gene-sets representing known biological and metabolic pathways were derived from 9 data resources, catalogued by and obtained from the MsigDB version 5.2²⁹ ([see URLs](#))
2. gene expression values from 53 tissues obtained from GTEx⁴⁸, log2 transformed with pseudocount 1 after winsorization at 50 and averaged per tissue
3. cell-type specific gene expression in 24 types of brain cells, which were calculated following the method described in Skene et al.⁵³ and Coleman et al.³⁷ Briefly, brain cell-type expression data was drawn from single-cell RNA sequencing data from mouse brains. For each gene, the value for each cell-type was calculated by dividing the mean Unique Molecular Identifier (UMI) counts for the given cell type by the summed mean UMI counts across all cell types. Single-cell gene-sets were derived by grouping genes into 40 equal bins by specificity of expression.

These gene-sets were tested for association with the GWAS gene-based test statistics using MAGMA. We computed competitive *P*-values, which represent the test of association for a specific gene-set compared to other gene-sets. This method is more robust to Type I error than self-contained tests that only test for association of a gene-set against the null hypothesis of no association²⁵. The Bonferroni-corrected significance threshold was $0.05/7,323 \text{ gene-sets} = 6.83 \times 10^{-6}$. Conditional analyses were performed as a follow-up using MAGMA to test whether each significant association observed was independent of all others. The association between each gene-set was tested conditional on the most strongly associated set, and then - if any substantial ($p < 0.05/\text{number of gene-sets}$) associations remained - by conditioning on the first and second most strongly associated set, and so on until no associations remained. Gene-sets that retained their association after correcting for other sets were considered to be independent signals. We note that this is not a test of

association per se, but rather a strategy to identify, among gene-sets with known significant associations whose defining genes may overlap, which set(s) are responsible for driving the observed association.

Cross-Trait Genetic Correlation

Genetic correlations (r_g) between intelligence and 38 phenotypes were computed using LD score regression³⁹, as described above, based on GWAS summary statistics obtained from publicly available databases ([see URLs](#); **Supplementary Table 18**). The Bonferroni-corrected significance threshold was $0.05/38 \text{ traits} = 1.32 \times 10^{-3}$.

GWAS catalog lookup

We used FUMA to identify SNPs with previously reported ($P < 5 \times 10^{-5}$) phenotypic associations in published GWAS listed in the NHGRI-EBI catalog²⁸ which overlapped with the genomic risk loci identified in the meta-analysis. As an additional relevant phenotype of interest, we examined whether the genes associated with intelligence in this study (by FUMA mapping or GWAS) were overrepresented in a set of 1,518 genes linked to intellectual disability and/or developmental delay, as compiled by RegionAnnotator ([see URLs](#)). Many of these have been identified by non-GWAS sources and are not represented in the NHGRI catalog. We tested for enrichment using a hypergeometric test with a background set of 19,283 genomic protein-coding genes, as in FUMA. Manual lookups were also performed to identify overlapping loci/genes with known previous GWAS of intelligence.

Mendelian Randomization

To infer credible causal associations between intelligence and traits that are genetically

correlated with intelligence, we performed Generalized Summary-data based Mendelian Randomization²⁹ (GSMR; [see URLs](#)). This method utilizes summary-level data to test for causal associations between a putative risk factor (exposure) and an outcome by using independent genome-wide significant SNPs as instrumental variables. HEIDI-outlier detection was used to filter genetic instruments that show clear pleiotropic effects on both the exposure phenotype and the outcome phenotype. We used a threshold p-value of 0.01 for the outlier detection analysis in HEIDI which removes 1% of SNPs by chance if there is no pleiotropic effect. To test for a potential causal effect of intelligence on various outcomes, we selected traits in non-overlapping samples that showed significant genetic correlations (r_g) with intelligence. We tested for bi-directional causation by repeating the analyses while switching the role of each correlated phenotype as an exposure and intelligence as the outcome. For each trait, we selected independent ($r^2 < 0.1$), GWS lead SNPs as instrumental variables in the analyses. For traits with less than 10 GWS lead SNPs (i.e. the minimum number of SNPs on which GSMR can perform a reliable analysis), the GWS threshold was lowered to 1×10^{-5} , allowing a sufficient number of SNPs to conduct the reverse GSMR analysis for former smoker status, autism, and intracranial volume.

The method estimates a putative causal effect of the exposure on the outcome (b_{xy}) as a function of the relationship between the SNPs' effects on the exposure (b_{zx}) and the SNPs' effects on the outcome (b_{zy}), given the assumption that the effect of non-pleiotropic SNPs on an exposure (x) should be related to their effect on the outcome (y) in an independent sample only via mediation through the phenotypic causal pathway (b_{xy}). The estimated causal effect coefficients (b_{xy}) are approximately equal to the natural log odds ratio (OR) for a case-control trait²⁹. An OR of 2 can be interpreted as a doubled risk compared to the population prevalence of a binary trait for every SD increase in the exposure trait. For quantitative traits the b_{xy} can

be interpreted as a one standard deviation increase explained in the outcome trait for every SD increase in the exposure trait. This method can help differentiate the likely causal direction of association between two traits but cannot make any statement about the intermediate mechanisms involved in any potential causal process.

Data Availability Statement

Summary statistics will be available for download upon publication from <https://ctg.cncr.nl>.

Methods-Only References

- 34 Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190-2191, doi:10.1093/bioinformatics/btq340 (2010).
- 35 Peloso, G. M. *et al.* Phenotypic extremes in rare variant study designs. *Eur J Hum Genet* **24**, 924-930, doi:10.1038/ejhg.2015.197 (2016).
- 36 Purcell, S., Cherny, S. S. & Sham, P. C. Genetic Power Calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* **19**, 149-150 (2003).
- 37 Coleman, J. *et al.* Biological annotation of genetic loci associated with intelligence in a meta-analysis of 87,740 individuals. *Mol Psychiatry*, doi:10.1038/s41380-018-0040-6 (in press).
- 38 Konig, I. R., Loley, C., Erdmann, J. & Ziegler, A. How to include chromosome X in your genome-wide association study. *Genet Epidemiol* **38**, 97-103, doi:10.1002/gepi.21782 (2014).
- 39 Bulik-Sullivan, B. *et al.* An atlas of genetic correlations across human diseases and traits. *Nat Genet* **47**, 1236-1241, doi:10.1038/ng.3406 (2015).
- 40 Okbay, A. *et al.* Genome-wide association study identifies 74 loci associated with educational attainment. *Nature* **533**, 539-542, doi:10.1038/nature17671 (2016).
- 41 Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7, doi:10.1186/s13742-015-0047-8 (2015).
- 42 Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat Genet* **47**, 1228-1235, doi:10.1038/ng.3404 (2015).
- 43 Wang, K., Li, M. & Hakonarson, H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res* **38**, e164, doi:10.1093/nar/gkq603 (2010).
- 44 Boyle, A. P. *et al.* Annotation of functional variation in personal genomes using RegulomeDB. *Genome Res* **22**, 1790-1797, doi:10.1101/gr.137323.112 (2012).
- 45 Ernst, J. & Kellis, M. ChromHMM: automating chromatin-state discovery and characterization. *Nat Methods* **9**, 215-216, doi:10.1038/nmeth.1906 (2012).
- 46 Roadmap Epigenomics Consortium *et al.* Integrative analysis of 111 reference human epigenomes. *Nature* **518**, 317-330, doi:10.1038/nature14248 (2015).
- 47 Zhu, Z. *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat Genet* **48**, 481-487, doi:10.1038/ng.3538
<http://www.nature.com/ng/journal/v48/n5/abs/ng.3538.html#supplementary-information> (2016).
- 48 GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* **348**, 648-660, doi:10.1126/science.1262110 (2015).
- 49 Westra, H. J. *et al.* Systematic identification of trans eQTLs as putative drivers of known disease associations. *Nat Genet* **45**, 1238-1243, doi:10.1038/ng.2756 (2013).
- 50 Zhernakova, D. V. *et al.* Identification of context-dependent expression quantitative trait loci in whole blood. *Nat Genet* **49**, 139-145, doi:10.1038/ng.3737 (2017).

- 51 Schmitt, A. D. *et al.* A Compendium of Chromatin Contact Maps Reveals Spatially Active Regions in the Human Genome. *Cell reports* **17**, 2042-2059, doi:10.1016/j.celrep.2016.10.061 (2016).
- 52 Liberzon, A. *et al.* Molecular signatures database (MSigDB) 3.0. *Bioinformatics* **27**, 1739-1740, doi:10.1093/bioinformatics/btr260 (2011).
- 53 Skene, N. G. *et al.* Genetic Identification Of Brain Cell Types Underlying Schizophrenia. *bioRxiv*, doi:10.1101/145466 (2017).